EXPERT REVIEW OF ANTI-INFECTIVE THERAPY
https://doi.org/10.1080/14787210.2022.2046462

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ORIGINAL RESEARCH

Tocilizumab effectiveness in mechanically ventilated COVID-19 patients (T-MVC-19 Study): a multicenter real-world evidence

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ABSTRACT

Background: This study aimed to evaluate the effectiveness of tocilizumab in mechanically ventilated patients with coronavirus disease 2019 (COVID-19).

Research design and methods: This retrospective multicenter study included adults (≥18 years) diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swab, and requiring invasive mechanical ventilation during admission. Survival analyses with inverse propensity score treatment weighting (IPTW) and propensity score matching (PSM) were conducted. To account for immortal bias, we used Cox proportional modeling with time-dependent covariance. Competing risk analysis was performed for the extubation endpoint.

Results: A total of 556 (tocilizumab = 193, control = 363) patients were included. Males constituted the majority of the participants (69.2% in tocilizumab arm,74.1% in control arm). Tocilizumab was not associated with a reduction in mortality with hazard ratio [(HR) = 0.82,95% confidence interval (95%CI): 0.62–1.10] in the Inverse propensity score weighting (IPTW) analysis and (HR = 0.86,95% CI: 0.64–1.16) in the PSM analysis. However, tocilizumab was associated with an increased rate of extubation (33.6%) compared to the control arm (11.9%); subdistributional hazards (SHR) = 3.1, 95% CI: 1.86–5.16).

Conclusions: Although tocilizumab was not found to be effective in reducing mortality, extubation rate while on mechanical ventilation was higher among tocilizumabtreatedgroup.

ARTICLE HISTORY
Received 14 December 2021
Accepted 21 February 2022

KEYWORDS (MeSH)
Tocilizumab; mechanical ventilation; COVID-19; mortality; effectiveness

1. Introduction

In December 2019, a series of pneumonia cases secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and what is currently known as the novel coronavirus disease 2019 (COVID-19) were reported from Wuhan, China [1]. Owing to its nature of high and quick transmissibility, by March 11th, 2020, COVID-19 had become a pandemic disease [2,3]. As of

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Supplemental data for this article can be accessed here

June 2021, more than 180 million patients globally have been infected with SARS-CoV-2 and 3.9 million deaths have been reported [4]. In Saudi Arabia, 480,000 confirmed COVID-19 cases in 100 cities were reported, of which 7,744 patients have died [5].

COVID-19 is characterized by fever, cough, fatigue, shortness of breath, pneumonia, and other respiratory tract symptoms [6,7]. However, the severity of the disease can range from mild flu-like symptoms to a devastating course of disease requiring respiratory support and Intensive Care Unit (ICU) admission [8]. The binding of the virus to the airway epithelial cells in COVID-19 patients results in the activation and up-regulation of the innate and adaptive immune response and releases a large number of cytokines, including Interleukin-6 (IL-6) [8,9]. A correlation between COVID-19 and levels of IL-6 has been reported [10,11], suggesting the possibility of repurposing IL-6 inhibitors in the management of severe COVID-19.

Tocilizumab, a recombinant humanized anti-IL-6 receptor monoclonal antibody, has been approved for the treatment of severe chimeric antigen receptor T cell-induced cytokine release syndrome [12]. Several studies have demonstrated the clinical benefit of tocilizumab in severe COVID-19 cases [13–18], though this has not been consistent [15,16]. In the RECOVERY trial, the allocation to tocilizumab was associated with a significant reduction in 28-day mortality compared with usual care alone in patients on non-mechanical ventilation [rate ratio (RR) = 0.85; 95% confidence interval (CI): 0.76–0.94; $p = 0.003$] but not in patients on invasive mechanical ventilation; [RR = 0.93. 95% CI, 0.74 − 1.18] [18]. More generally, studies were limited due to heterogeneity in study designs, small sample sizes, diversity of study populations, variations in disease severity spectrum, wide ranges of dose regimen, and its frequency, differences in timing of starting tocilizumab therapy, and limiting results to pooled crude unadjusted estimates.

A recent meta-analysis of 25 trials revealed an association of tocilizumab with a reduction in overall mortality [odds ratio (OR) = 0.70, 95% CI, 0.54–0.90, $P = 0.007$], and mechanical ventilation requirement [OR = 0.59, 95% CI, 0.37–0.93, $P = 0.02$] [19]. These studies were conducted in different countries including the United States, United Kingdom, Canada, Italy, and Spain, but none of these studies were conducted in Saudi Arabia or the Middle East. Additionally, the contradicting data challenge the decision-makers in determining optimal clinical practice for tocilizumab. In this study, we aimed to evaluate the effectiveness of tocilizumab in COVID-19 mechanically ventilated patients in daily clinical practice in Saudi Arabia at the height of the early pandemic.

2. Patients and methodS

2.1. Study design and setting

This was a retrospective study conducted in six centers in three cities in Saudi Arabia: King Saud Medical City Hospital (KSMC) in Riyadh, King Fahad Medical City (KFMC) in Riyadh, King Saud University Medical Center (KSUMC) in Riyadh, Prince Mohammad bin Abdulaziz Hospital (PMAH) in Riyadh, King Faisal Specialist Hospital and Research Center (KFSH&RC) in Jeddah, and Almoosa Specialist Hospital in Al-Ahsa.

The study was approved by the following Institutional Review Board Committees (IRB) with waived informed consent: King Saud Medical City (IRB# H-01-R-053), Second Health Cluster Institutional Review Board (IRB# H-01-R-012), King Saud Medical University Institutional Review Board (IRB# E-20-5527) and Almoosa Specialist Hospital Institutional Review Board (IRB# ARC-20.10.2). We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement checklist in our report [20]. All methods were carried out in accordance with relevant guidelines and regulations.

2.2. Participant selection

We obtained lists of severely/critical ill COVID-19 patients or those who received tocilizumab treatment between March 2020 to January 2021. Through a random-selection process, we screened patients for eligibility. The random selection would minimize sampling bias and provide an equal opportunity for the patient's record to be selected and coded [21]. Inclusion criteria were as follows: age ≥18 years, diagnosis of SARS-CoV-2 by real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swab, and requiring invasive mechanical ventilation at admission. Patients were excluded if they were outside the study period, did not require mechanical ventilation, or received tocilizumab treatment for an indication other than COVID-19.

2.3. Tocilizumab dosing

Tocilizumab was dosed according to Saudi Ministry of health (MOH) protocols version 2.0 updated in June 2020. The adult dosing for tocilizumab was 4–8 mg/kg (usual dose 400 mg; maximum 800 mg) by IV infusion; repeated within 12 hours for a maximum of 2 doses [22].

2.4. Data collection

Data were manually extracted from electronic health records (EHRs) and then entered into the Research Electronic Data Capture (REDCap) system in a de-identified manner [23]. A trained team of data managers ensured the quality of data collection and resolved any discrepancies.

2.5. Objectives/study outcomes

The aim was to assess tocilizumab effectiveness in mechanically ventilated COVID-19 patients as compared to a control group that did not receive tocilizumab. The primary endpoint was mortality after mechanical ventilation (referred to here as overall mortality). The secondary endpoint was the rate of extubation. Subgroup analyses for the mortality outcome based on baseline characteristics were explored. We also explored the association between time of tocilizumab administration and mortality.

2.6. Sample size calculation

Assuming a – 10% risk difference in the overall mortality between the tocilizumab and control arms, a sample size of 489 (166 patients who received tocilizumab and 332 who were unexposed to tocilizumab with an estimated ratio of 1:2) assured a power of 80% after applying continuity correction. A significance level (α, type 1 error rate) of 5% was applied.

2.7. Statistical analysis

2.7.1. Statistical software used

We used R Core Team (2020) software (R Foundation for Statistical Computing, Version 4.0.1, Vienna, Austria. The following packages in the R interface were used to conduct the analyses: survival [24], ggplot2 [25], survminer [26], survey [27], mice [28], matchThem [29], cobalt [30], crrSC [31].

Descriptive statistics was used to present baseline characteristics. Continuous data were presented as means with standard deviations (±SD) and medians with interquartile ranges (IQRs). Student's *t*-test or Mann–Whitney *U* test was used for between-arm comparison.

Categorical data were reported as frequencies and percentages and analyzed using either the Chi-square test for nxm tables or Fisher's exact test for 2×2-table group comparisons. Missing data were determined to be missing at random (MAR) and handled by Multiple Imputation by Chained Equations (MICE) procedure with Nelson Aalen estimator [28,32]. We only considered variables that had <15% of their data missing. Fifty imputations were obtained for the missing value (5 imputed datasets with 10 iterations).

Due to the observational design and the presence of many confounders, we implemented propensity score-based methods to estimate the marginal treatment effect. First, we carried out the inverse propensity score treatment weighting (IPTW) procedure. In IPTW, propensity scores (probability of getting a treatment) were calculated from a multivariable logistic regression model that included all the covariates of interest. Correlation testing was conducted to avoid the inclusion of highly correlated variables in the models. Next, propensity scores were used to calculate weights based on Desai and Franklin formulas [33] using the average treatment effect among the treated (ATT) as the target estimand (i.e. the 'ideal' patients for tocilizumab treatment based on specific characteristics). Balance between arms was achieved by creating a pseudo-population in which treatment allocation was independent of the observed covariate. To handle extreme weights, we utilized weight trimming (truncation) and stabilization. Balance of the covariates was checked by standardized mean difference (SMD) and love plots. SMD values <0.2 indicated a good balance. Propensity scores distributions were illustrated by mirror diagrams. As weighting may inflate or deflate the sample size relative to the original population; therefore, a robust sandwich-type estimator for variance estimation was calculated using 'survey' package in R for the treatment effect estimates [34].

After weighting and using this package, we fitted an adjusted (weighted) Kaplan-Meier (KM) model to estimate the probability of survival after mechanical ventilation (time 0) in both arms. Events were censored if patients were discharged alive or were still intubated at the time of data collection. A log rank test that accounted for the weighted data was applied to detect differences in survival curves.

To estimate the relative treatment effect, a Cox proportional model was fitted on the weighted data with the arm as a single covariate using the 'survey' package for robust variance estimation. The estimate was subsequently pooled across the imputed datasets. Proportional hazard assumption was checked by Schoenfeld residuals plots and statistical testing.

2.7.2. Sensitivity analyses

2.7.2.1. Propensity score matching. Propensity scores matching (PSM) was performed to confirm the results from the IPTW analysis. Propensity scores were generated from the same logistic regression model used in the IPTW model, which included all variables of interest. We then used the nearest-neighbor matching within the imputed datasets approach (using Rubin's rules) [35] and 1:2 ratio with a caliper of 0.2 [36] and no replacement. Adequate balance of the data was checked by SMD (<0.2 desirable). Visual diagnostics such as love plots for covariate balance and mirror plots for propensity score distributions were generated. Next, we fitted a KM model to the matched data to compare survival probabilities after mechanical ventilation. To test for the statistical difference in the survival curves, we performed a stratified log rank test [37]. For relative treatment effect, a Cox proportional hazard model was fitted using the matched dataset. To account for the paired nature of the data, we stratified on the matched pairs and a robust variance was estimated using the 'survey' package.

2.7.2.2. Immortal time bias. The study design may entail a potential immortal time bias. In randomized control trials, the time of treatment assignment and time 0 is aligned. This was not possible in our case as patients may have started tocilizumab treatment after a few days of mechanical ventilation (time 0). During this period, the patient must be alive to receive the treatment later (i.e. immortal bias). The person-days during which patients in the tocilizumab arm did not receive treatment should be accounted toward the untreated group. A Cox proportional hazard model with time dependency covariance was used to evaluate a possible immortal time bias. We performed these analyses with the propensity score-based procedures (IPTW and PSM).

2.7.2.3. Competing risk analysis. For the secondary outcome (extubation), we performed a competing risk analysis for death while on mechanical ventilation; specifically, patients who die while on mechanical ventilation cannot experience the extubation event. The cumulative incidence function (CIF) was estimated using a cluster Fine-Gray model to derive the sub-distribution hazard ratio (SHR): the instantaneous risk of failure from an event in subjects who have not failed that type of an event [38]. In the case of the extubation outcome, a SHR>1 indicated a higher incidence probability of the event occurring in tocilizumab. Following the recommendation by Austin et al.,

we conducted the analysis on the matched dataset using the CrrSC package in R to account for the matched pairs [39]. The cause-specific hazard ratio (CSHR) was also estimated as part of the competing risk analysis as suggested by Latouche et al. by fitting Cox proportional models on the matched dataset [40]. Cause specific hazards refers to the instantaneous rate of the outcome of interest in subjects who are event-free. In the case of extubation outcome, a cause specific hazard ratio (CSHR) values of >1 meant a relative increase in the instantaneous rates of extubation rates favoring the tocilizumab arm. The CIF was plotted for each arm and competing risk.

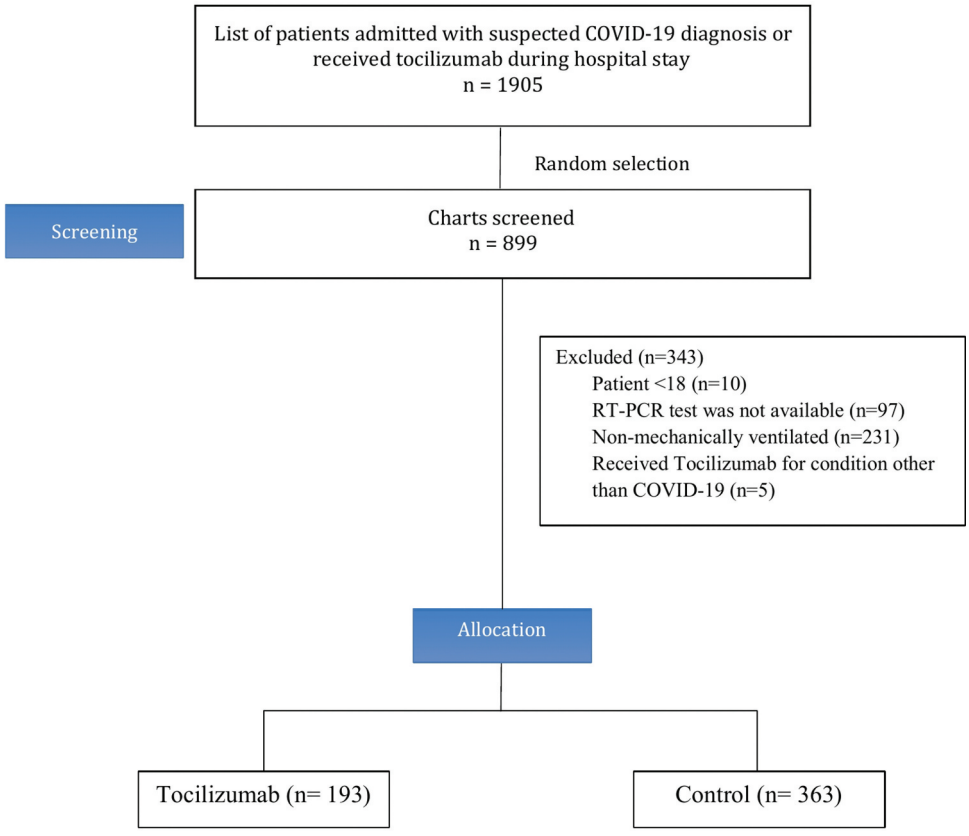
2.7.2.4. Additional analyses. We investigated the association between the time of tocilizumab administration and overall mortality. Using both propensity score approaches (IPTW and PSM), a logistic regression model was fitted that included time of administration as a covariate (prior mechanical ventilation, or within 48 hours and >48 hours of mechanical ventilation) versus control as a reference. We also conducted subgroup analyses to examine the baseline characteristics as treatment effect modifiers of overall mortality using the matched dataset.

3. Results

A total of 899 patients were screened for inclusion eligibility (Figure 1). We excluded 334 patients for various reasons, the most common one was not being on mechanical ventilation at admission (n = 231). We included 193 patients in the tocilizumab and 363 patients in the control arm.

Overall, there were no differences in the baseline characteristics of age, gender, weight, body mass index (BMI), kidney function and comorbid conditions such as hypertension, diabetes, cardiovascular disease. However, differences were observed in terms of ethnicity (P = 0.044); solid organ transplant (P= 0.025); medication used in the hospital prior to ICU admission such as favipiravir (P < 0.001), hydroxychloroquine (<0.001), therapeutic anticoagulation (<0.001), and convalescent plasma therapy (P < 0.001). More patients in the tocilizumab arm had a fever at the time of intubation (P = 0.030) and presented with a lower median partial oxygen pressure to fractional inspired oxygen (paO2/Fio2) ratio (71.1 versus 102.0 in the control arm). Arms also differed in terms of the following laboratory variables: albumin, aspartate aminotransferase, lactate dehydrogenase, ferritin, sodium, potassium, and magnesium. Variables with the highest missing data were alkaline phosphatase (35%) and erythrocyte sedimentation rate (41.2%) (see Table 1 footnote)

The IPTW and PSM mirror plots for propensity score distribution were presented in Figures S1 and S2 and the Love plots for covariate balance for both IPTW and PSM in Figure S3 and Table S1, all showing adequate balance. Of the patients in the tocilizumab arm, 21.2% of received the treatment within



COVD-19: coronavirus disease 2019. RT-PCR: real-time polymerase chain reaction.

Figure 1. Patients selection flowchart.

Table 1. Baseline characteristics.

Characteristic	Tocilizumab (n = 193)	Control (n = 363)	P value
Age, mean (±SD)	59.3 (14.2)	58.5 (13.7)	0.515
Female, *n* (%)	61 (30.8)	91 (25.1)	0.143
Ethnicity, ***n*** (%)			0.044
• Middle Eastern	137 (69.2)	230 (63.4)	
• East/Southeast Asian	14 (7.1)	15 (4.1)	
• South Asian	39 (19.7)	86 (23.7)	
• African	5 (2.5)	28 (7.7)	
• Unknown/other	3 (1.5)	4 (1.1)	
Weight (kg), median (IQR)	80.0 (70.0–95.0)	80.0 (70.0–92.0)	0.514
BMI (kg/m^2), median (IQR)	29.4 (26.0–34.3)	29.1 (25.0–33.2)	0.059
Scr (mg/dl), median(IQR)	0.98 (0.76–1.62)	1.04 (0.77–1.81)	0.314
CKD-EPI (mL/min/m^2), median (IQR)	77.7 (42.1–98.9)	75.3 (37.9–97.8)	0.539
CKD stage, ***n*** (%)			0.884
• Normal/Stage1	75 (37.9)	123 (33.9)	
• Stage 2	49 (24.7)	92 (25.3)	
• Stage 3A	20 (10.1)	37 (10.2)	
• Stage 3B	16 (8.1)	30 (8.3)	
• Stage 4	24 (12.1)	39 (10.7)	
• Stage 5	14 (7.1)	35 (9.6)	
• Unknown	0 (0.0)	7 (1.9)	
Respiratory diseases, *n* (%)	18 (9.1)	43 (11.8)	0.316
Established cardiovascular diseases, *n* (%)	21 (10.6)	45 (12.4)	0.529
Atrial fibrillation, *n* (%)	6 (3.0)	10 (2.8)	0.851
History of VTE, *n* (%)	3 (1.5)	5 (1.4)	1.000
Type 1 or 2 Diabetes, *n* (%)	107 (54.0)	207 (57.0)	0.496
Hypertension, *n* (%)	117 (59.1)	196 (54.0)	0.245
Dyslipidemia, *n*(%)	12 (6.1)	34 (9.4)	0.172
Liver disease, *n* (%)	3 (1.5)	6 (1.7)	1.000
History of cancer, *n* (%)	7 (3.5)	7 (3.5)	0.243
Solid organ transplant, *n* (%)	6 (3.0)	2 (0.6)	0.025
HIV, *n* (%)	1 (0.5)	0 (0.0)	0.352
ECMO, *n* (%)	4 (2.0)	13 (3.6)	0.440
Time of mechanical ventilation relative to admission, ***n*** (%)			0.122
• <24 hours	45 (22.7)	77 (21.2)	
• 24–48 hours	29 (14.6)	66 (18.2)	
• >48 hours	118 (59.6)	194 (53.4)	
• Outside transfer on mechanical ventilation	6 (3.0)	26 (7.2)	
Medication use during hospitalization, ***n*** (%)			
• ACEI or ARB	31 (15.7)	63 (17.4)	0.607
• Statins	72 (36.4)	102 (28.1)	0.043
• Azithromycin	142 (71.7)	279 (76.9)	0.178
• Favipiravir	103 (52.0)	60 (16.5)	<0.001
• Hydroxychloroquine	20 (10.1)	14 (3.9)	0.003
• Lopinavir/Ritonavir	16 (8.1)	31 (8.5)	0.851
• Ribavirin	14 (7.1)	24 (6.6)	0.836
• Interferon B	9 (4.5)	18 (5.0)	0.827
• Steroid	192 (97.0)	347 (95.6)	0.421
• Vitamin C	102 (51.5)	203 (55.9)	0.316
• Thiamine	45 (22.7)	172 (47.4)	<0.001
• Vitamin D	126 (63.6)	228 (62.8)	0.846
• Zinc	136 (68.7)	233 (64.2)	0.283
• Vasopressors/Inotropes	160 (80.8)	307 (84.6)	0.253
• Therapeutic anticoagulant	148 (74.7)	218 (60.1)	<0.001
• Convalescent plasma therapy	9 (4.5)	1 (0.3)	<0.001
Baseline vitals and labs at the time of intubation			
• Fever, *n* (%)	16 (8.1)	52 (14.3)	0.030
• WBC (10^3/μL), median(IQR)	12.9 (8.0–16.1)	12.4 (9.3–16.8)	0.194
• Lymphocyte count (cells/μL), median(IQR)	790.0 (530.0–1270.0)	751.5 (496.3–1130.0)	0.150
• Hgb (g/dL), median (IQR)	12.8 (10.9–14.0)	12.8 (10.6–13.9)	0.208
• Platelets (per 10^9/L), median (IQR)	235.0 (186.0–314.0	249.0 (189.0–327.0)	0.161
• Pao2/Fio2, median (IQR)	72.1 (50.0–93.2)	102.0 (73.0–166.0)	<0.001
• Albumin (g/dL), median (IQR)	3.0 (2.7–3.3)	2.8 (2.5–3.2)	<0.001
• Total bilirubin (μmol/L), median(IQR)	9.3 (6.3–12.9)	10.2 (7.1–14.5)	0.030
• AST (U/L), median (IQR)	47.0 (36.0–75.0)	57.5 (38.0–96.2)	0.010
• ALT (U/L), median (IQR)	46.0 (27.0–69.4)	42.0 (27.0–73.5)	0.718
• ALP (U/L), median (IQR)	96.4 (69.0–135.7)	104.0 (72.8–150.9)	0.101
• LDH (U/L), median (IQR)	724.0 (550.0–1116.0)	616.0 (446.0–854.0)	<0.001
• Ferritin (μg/L), median (IQR	1292.7 (670.0–2446.6)	1074.0 (526.2–2000.0)	0.018
• ESR (mm/hr), median (IQR)	67.0 (27.2–85.5)	68.5 (45.0–98.3)	0.133
• CRP (mg/dL), median (IQR)	103.1 (36.6–180.9)	137.0 (73.0–160.0)	0.060
• D-dimer (μg/mL), median (IQR)	2.3 (1.2–7.3)	2.6 (1.4–6.8)	0.545
• Sodium (mmol/L), median (IQR)	137.0 (134.0–142.0)	139.0 (136.0–144.0)	0.002
• Potassium (mmol/L), median (IQR)	4.2 (3.8–4.5)	4.3 (3.9–4.8)	0.004
• Calcium (mmol/L), median (IQR)	2.0 (3.8–4.5)	2.0 (3.9–4.8)	0.844
• Magnesium (mmol/L), median (IQR)	0.89 (0.79–1.0)	0.92 (0.81–1.0)	0.015

BMI: body mass index. Scr: serum creatinine. CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration. Established cardiovascular disease was defined as a documented history of stable angina, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft surgery, or myocardial infarction (MI). Heart failure and cerebrovascular disease included transient ischemic attack (TIA) or stroke. Respiratory disease: asthma or chronic obstructive pulmonary disease (COPD). VTE: venous thromboembolism. HIV: human immunodeficiency virus. ECMO: extracorporeal membrane oxygenation. NSAIDs: nonsteroidal anti-inflammatory drugs. ACEI: angiotensin-converting enzyme inhibitors. ARB: angiotensin receptor blockers. WBC: White blood cells. Hgb: Hemoglobin. Pao2: partial pressure of oxygen. FiO2: fraction of inspired oxygen. AST: aspartate aminotransferase. ALT: Alanine transaminase. ALP: Alkaline phosphatase. LDH: Lactate dehydrogenase. ESR: erythrocyte sedimentation rate. CRP: c-reactive protein. IQR: Interquartile range

Missing data (%): potassium, WBC, BMI (<1%). Pao2/Fio2, CKD epi, Scr, platelet, albumin (1–2%). Total bilirubin, lymphocyte count, magnesium, LDH (2–5%). AST,d-dimer (5–8%). Calcium (9.3%). CRP (12.4%). Ferritin (14.3%). ALP (35%). ESR (41.2%)

48 hours and 25.7% received the treatment after 48 hours of mechanical ventilation. Proportionately more patients (60.6%) received two doses of tocilizumab with a median dose of 8 mg/kg/day (Table S2).

3.1. Overall mortality outcome

The overall death rate in the control arm (81.1%) was higher compared to the tocilizumab arm (62.6%). The IPTW analysis examining the two adjusted survival curves showed a difference in the absolute effect (log rank test, $P = 0.033$; Figure 2a). As for the relative treatment effect, tocilizumab was associated with a lower incidence of mortality with HR = 0.73 (95%CI 0.55–0.96, $P = 0.026$). However, the PSM analyses did not confirm the IPTW results. No differences between the survival curves (Figure 2b, stratified log rank test $P = 0.900$) and in the relative treatment effects was observed (HR = 0.80, 95% CI 0.57-1.12, $P = 0.192$). When accounting for immortal time bias with Cox time dependent covariance, both the IPTW (HR = 0.82, 95%CI 0.62–1.10, $P = 0.190$) and the PSM (HR = 0.86, 95%CI of 0.64–1.16, $P = 0.349$) analyses showed no difference in overall mortality between the two arms (Table 2; Figure 3).

3.2. Competing risk analysis

A higher percentage of patients experienced extubation in the tocilizumab arm (33.6%) versus the control arm (11.9%). When compared to the control, the CSHR for the extubation outcome for tocilizumab was 2.72 (95% CI 1.56–4.76, $P < 0.001$) and the subdistribution hazard ratio (SHR) was 3.1 (95% CI 1.86–5.16, $P < 0.001$) from the Fine-Gray model. Whereas there was no significant result for death on the mechanical ventilation outcome with CSHR of 0.98 (95% CI 0.70–1.38, $P = 0.927$) but a significant result for the Fine-Gray model with a SHR of 0.68 (95% CI 0.511–0.901, $P = 0.007$). The results of the competing risk analysis were presented in Table 3 and the cumulative incidence function visualized in Figure 2c.

Table 2. Overall mortality outcome after mechanical ventilation.

Analysis	Propensity Score Weighting (Trimmed IPTW ATT)	Propensity Score matching
Outcome	Tocilizumab (n = 198) vs control (n = 365)	Tocilizumab (n = 137) vs control (n = 176)
Overall deaths, n (%)	122 (62.6) vs 269 (81.1)	82 (59.9) vs 125 (72.2)
Adjusted log-rank test/stratified log-rank test†	0.033	0.900
Overall Mortality, HR (95%CI)[a]	0.73 (0.55– 0.96, $P = 0.026$)	0.80 (0.57–1.12, $P = 0.192$)
Overall mortality when accounting for Immortal bias, HR (95%CI)‡	0.82 (0.62–1.10, $P = 0.190$)	0.86 (0.64–1.16, $P = 0.349$)

IPTW: Inverse propensity score weighting.
ATT: Average treatment effect on the treated
PSM: Propensity score matching
CI: Confidence interval
HR: Hazard ratio
† Survey package (svykm function) used to estimate the survival function with weighted Kaplan-Meier estimator (adjusted curves). For the stratified log-rank test, we performed the analysis on the matched dataset stratifying on the matched pairs.
‡Extended cox time dependency models that accounted for immortal bias by using T_{merge} function in the survival package.
[a]95% Confidence interval was calculated using robust-type variance estimator using survey package.

3.3. Subgroup analysis results

No association between the time of tocilizumab administration and overall mortality was found (Table S3). The subgroup analyses for effect modifiers based on baseline characteristics showed interaction effects only for chronic kidney disease stage, angiotensin converting enzyme inhibitor (ACEIs) or angiotensin receptor blocker use (ARBs), and Pao2/Fio2 ratio (>100 versus <100), but not for any other variables (see Figure S4).

4. Discussion

Therapeutic management of COVID-19 is evolving and expanding, with several treatments having been approved, mainly under the emergency use authorization provision (EUA) [41–43]. Among them, onlydexamethasone and tocilizumab have shown survival benefits, yet not consistently so across disease spectrums nor across studies [6,44–46]. The association between cytokine release syndrome and COVID-19 severity sparked an interest in the three available anti-IL-6 monoclonal antibodies (tocilizumab, sarilumab, and siltuximab) [47,48]. Of these, tocilizumab has received the most interest due to its availability and the experience gained since its approval in 2008 [49]. Considering the accumulated evidence, tocilizumab was authorized for the treatment of COVID-19 in a special patient population and has been incorporated in the treatment guidelines, including for patients with rapid respiratory decompensation [22]. Our study differs from prior published studies in that it included only mechanically intubated and examined whether tocilizumab is effective in reducing mortality and increasing ventilator independency (extubation) compared to standard care. Although both the IPTW and PSM analyses showed that tocilizumab was effective in reducing mortality, this statistical significance was lost when we accounted for immortal time bias. These findings are in concordance with several recent studies [18,46,50–52]. Conversely, in a study in mechanically intubated COVID-19

Table 3. Competing risk analysis for the clinical outcomes.

Crude outcomes	Tocilizumab (n = 137) vs control (n = 176)
Extubation events, n (%)	46 (33.6) vs 21 (11.9)
Death on MV, n (%)	79 (57.7) vs 122 (69.3)
Cause specific hazard regression model	
Extubation, CSHR (95%CI, P value)	2.72 (1.56–4.76, $P < 0.001$)
Death on MV, CSHR (95%CI, P value)	0.98 (0.70–1.38, $P = 0.927$)
Fine-Gray model †	
Extubation, SHR (95%CI, P value)	3.1 (1.86– 5.16, $P < 0.001$)
Death on MV, SHR (95%CI, P value)	0.68 (0.51 to 0.90, $P = 0.007$)

All analyses were conducted on the matched dataset.
† Competing risk analysis conducted using Fine-Gray model on the matched dataset using crrSC package to account for the matched pairs.
‡ Statistical test to compare cumulative incidence function curves
MV: Mechanical Ventilation
CSHR: Cause specific hazard ratio
SHR: Subdistribution hazard ratio

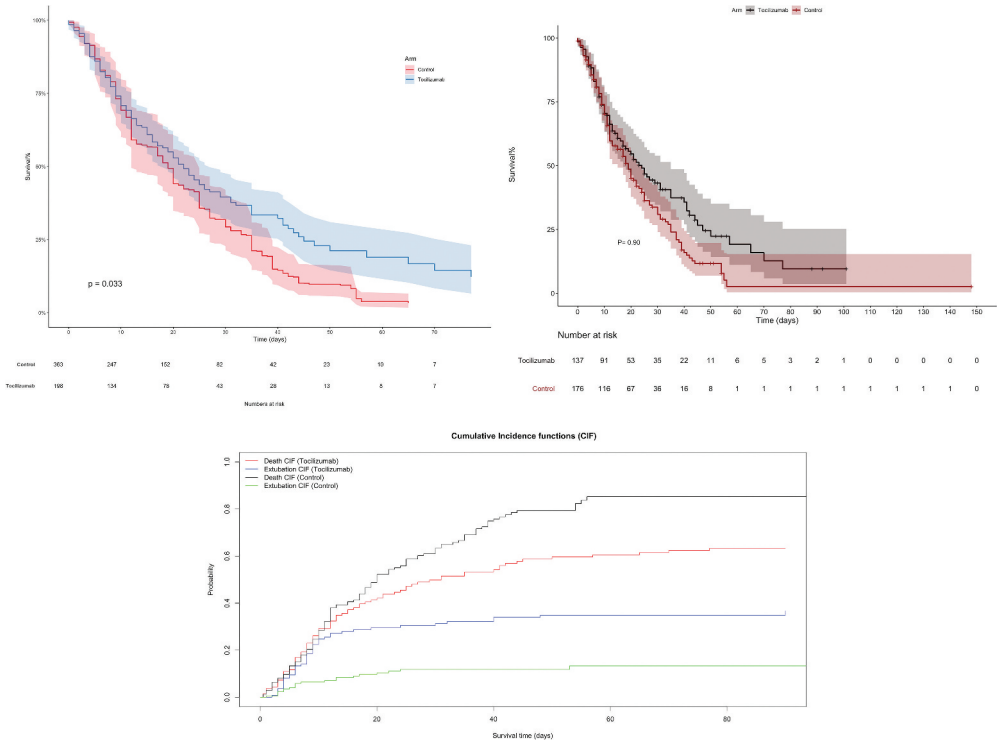
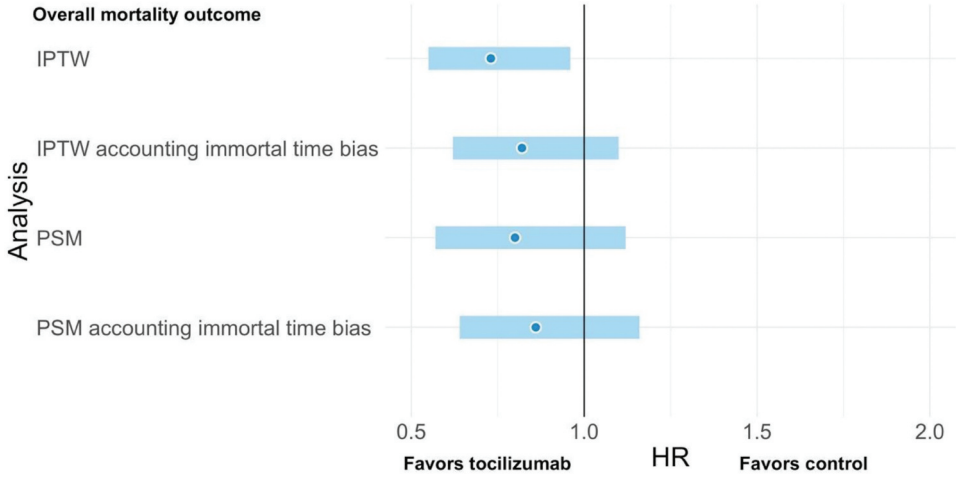


Figure 2. Kaplan Meier curves for overall mortality. (a) Inverse propensity score treatment weighting. (b) Propensity score matching. (c) Cumulative incidence function for the competing risks while on mechanical ventilation.



IPTW: Inverse propensity score treatment weighting. PSM: Propensity score matching. HR: Hazard ratio

Figure 3. Forest plot of hazard ratios with their corresponding 95% confidence interval obtained from the conducted analyses.

patients, Somers and colleagues found that exposure to tocilizumab was associated with a reduction in mortality by 45% [53]. However, more than 40% of patients in the tocilizumab arm were treated 24 hours after intubation, which may have introduced a misclassification bias [54]. Similar to our study, the authors balanced the tocilizumab and control groups using IPTW [53]. In other studies with analyses similar to ours, neither steroids nor PaO2/FiO2 were included in the propensity score model [55]; or patients who died before receiving tocilizumab were excluded, thus possibly inducing selection bias [54]. Further, and although their study was not restricted to mechanically ventilated patients, Biran and colleagues [56] observed that tocilizumab was associated with a reduction in mortality by 29%. Here too, the mortality benefit was lost after adjusting for immortal time bias. A recent meta-analysis published by the World Health Organization (WHO) Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group aimed to synthesize the evidence on IL-6 inhibitors exposure and mortality [57]. While the overall analysis showed that IL-6 inhibitors were associated with

reduction in mortality, the subgroup analysis of mechanically ventilated patients didn't favor IL-6 inhibitors when compared to control.

The absence of an unequivocal mortality benefit in our study may be explained by two factors. First, initiating an immunomodulator at a later stage of the cytokine release syndrome may be less effective than initiating it at an earlier stage. The mortality benefit observed with tocilizumab was observed mainly in patients with moderate to severe COVID-19 who did not require mechanical ventilation [56,58–61]. Russell and colleagues in a multicenter retrospective study comparing early (prior to or within 24 hours of intubation) versus late tocilizumab (more than 24 hours after intubation) administration, found that early administration was associated with a 85% reduction in mortality when compared to no tocilizumab [62]. In addition to the small sample size, it is worth noting that the matching model included only a few variables, which could have decreased the precision of the exposure effect [63,64]. In our study, the majority (72%) received tocilizumab within 48 hours of intubation (Table S2) with no differences in mortality regardless of the timing of administration (Table S3). Though subject to further investigation in a randomized controlled trial, because of its larger sample size and the rigorous differentiated statistical analyses, our study provides initial evidence of no mortality benefit with early tocilizumab administration. Second, despite the evidence of IL-6 as a proinflammatory cytokine involved in cytokine release syndrome, other proinflammatory cytokines may also be involved and might mediate or moderate outcomes in worsening COVID-19 patients [48]. The potential benefit of using other immunomodulators against these cytokines should be examined under controlled conditions as well as in the setting of daily clinical practice.

With regard to our results related to the extubation rate, we performed a competing risk analysis to account for events that might compete with this secondary study outcome (i.e. death on mechanical ventilation). The addition of tocilizumab reduced the hazard of COVID-19 patients to remain intubated by 172% (CSHR: 2.72). Our findings differ from those of a retrospective study by Fisher and colleagues in which the extubation rate in tocilizumab arm was similar to that in the control arm (OR 1.53; 95% CI, 0.71 − 3.30) [52]. An important difference in our study is that patients treated with tocilizumab received more concurrent medications (notably, favipiravir and convalescent plasma) compared to those in the study by Fisher and colleagues. Despite the equivocal results on the primary outcome of interest, our study underscores the importance of a number of methodological and analytical issues that need to be addressed, especially in critical care studies. One is the importance of sensitivity analyses. Our IPTW analysis on the primary outcome was subjected to a sensitivity analysis using PSM – which, in fact, failed to confirm the IPTW results. This discrepancy could be attributed to several factors. The IPTW analysis included more observations compared to the PSM analysis. It yielded a much narrower 95% CI and therefore greater precision of the estimate. It is also possible that the IPTW analysis may have been prone to model misspecification compared to PSM model. However, covariate balance diagnostics showed that all variables in IPTW analysis had adequate balance as indicated by the SMD, yet that the PSM model had less bias for the overall distance.

Further, we accounted for immortal time bias by counting the person-days where no treatment was received in the tocilizumab group toward the untreated group using Cox time dependent covariance. Here, neither the IPTW nor the PSM analyses found a difference in the overall mortality. Immortal bias is an analytical procedure common in observational studies [65]. It refers to a period of time in which patients must be alive to receive the treatment. If our study were a randomized control trial, the time of tocilizumab administration (i.e. treatment allocation) should be aligned with the mechanical ventilation (day 0) to avoid misclassification of the exposure. However, in observational studies, patients may start their treatment at different time points after day 0. Consider, for instance, the scenario where time 0 for the tocilizumab group is when treatment is started and time 0 for the control group is the time of starting mechanical ventilation. Excluding immortal time induces selection bias in that person days that should have been counted as untreated are excluded, shortening the person days for the untreated, and thus biasing the estimate. To avoid the ensuing misclassification of the exposure, treatment should be considered a time-dependent rather than a fixed-time covariate to ensure that all person days will be correctly counted toward the treated or untreated arms [54]. Our decision to control for immortal time bias is underscored by a study by Shinati et al. in mechanically ventilated ICU patients. Fixed time analysis yielded a strong association of ICU length stay and delirium but this association was not found when considering delirium as a time dependent covariate.

A competing risk analysis was conducted for our secondary extubation outcome. Koller and colleagues reviewed 50 publications in high-impact journals and reported that 70% of these publications were susceptible to competing risk problems [66]. Competing risks occur when the occurrence of an event may prevent the occurrence of the primary event of interest [38]. In critical care settings, the extubation endpoint, while an important marker of patient improvement, may also be affected by rapidly changing changes in status due to new events occurring that are unrelated to the treatments of interest. Further, there is a common misconception that hazard ratios derived from competing risk models convey the same information (Fine-Gray Model versus Cause-specific hazard (CSH) model); while, in fact, this is not the case. The CSH model evaluates a binary event of interest over time, considers all other events as non-relevant, therefore censors these events, and thus violates the assumption of non-informative censoring. When there are no competing risks, the survival function can be linked directly with the hazard function and the CIF can be calculated as 'one minus survival function.' However, in the case of competing risks, there is no direct one-to-one link between survival and hazard function. Therefore, a naïve KM estimator will be larger than an estimator that accounts for other competing risks. To estimate the impact of covariate of interest on CIF in the presence of

competing risks, the use of Fine-Gray models is recommended [38,67]. In our CSH analysis, the extubation rate was much higher in the tocilizumab arm. Likewise, the probability of event occurrence was also higher in our Fine-Gray model. However, the event of death on mechanical ventilation had a statistical non-significant CSHR result but a statistically significant SHR result. One interpretation, though an erroneous one, would be that patients treated with tocilizumab treatment have a lower probability of death while on mechanical ventilation. There was indeed a seemingly greater impact of extubation events on the CIF, which in turn had an indirect impact on the CIF for the competing risk outcome of death on mechanical ventilation. This made it appear that tocilizumab had an exclusive protective effect against death while on mechanical ventilation (MV) – when, in fact, extubated patients cannot experience death while on MV. That is why Latouche and colleagues recommend to report both CSH and Fine-Gray models side by side for competing risk analysis. This allows transparency and facilitates interpretation of the results [40]. One caveat for using Fine-Gray models is that statistical methods accounting for time varying covariance are not well established yet and need further research [68].

Our study has some limitations. It was observational and may have included potential confounders. Hence our decision to apply two propensity score methods to control for bias reduced unmeasured confounding [69]. Although we included many variables in our propensity score models, variables that predict ICU mortality such as the Sequential Organ Failure Assessment (SOFA) or the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHEII) scores were not available in or calculable from the medical records. Having these aggregate metrics available, as opposed to using the individual components of these scores (in as far as available, as we did), places the propensity score models at risk of overfitting. The competing risk analysis did not consider immortal time bias as the inclusion of time-dependent variables in Fine-Gray models is less established and is an area of ongoing statistical research. The recent evidence suggests that clinical improvement or reduction in mortality following exposure to tocilizumab could be seen in patients with elevated IL-6 levels [70,71]. In our institutions, IL-6 levels were not readily available; however, the following biomarkers were measured: ferritin, c-reactive protein (CRP), and D-Dimer (Table 1). Importantly, CRP levels are predictive of IL-6 mediated disease severity [72,73], hence absence of IL-6 levels should not adversely impact the findings of our study. As shown in figure S4 subgroup analysis, we found no interaction in patients with CRP (mg/dL) ≥75 or <75. Additionally, and per MOH COVID-19 treatment guidelines, one or more of the aforementioned biomarkers could be used to predict cytokine syndrome and thus indication for tocilizumab [74].

5. Conclusions

This current study suggests that tocilizumab was not effective in reducing mortality. After accounting for immortal time bias, there were no differences between IPTW and PSM in terms of the absolute effect. However, extubation rate while on mechanical ventilation was higher among tocilizumab-treated patients, indicating a possible benefit in this patient population. A randomized controlled trial evaluating tocilizumab against standard of care in critically ill mechanically ventilated patients is needed.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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